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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/302,434	04/30/1999	KLAUS BOSSLET	026083/0119	6895

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EXAMINER
HUNT, JENNIFER ELIZABETH

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/302,434	Applicant(s) Bosslet et al.
	Examiner Jennifer Hunt	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Nov 28, 2001* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *22-65* is/are pending in the application.

4a) Of the above, claim(s) *22-36 and 59-65* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *37-58* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

Response to Amendment

1. Claims 22-65 are pending in the application. Claims 22-36 and 59-65 have been withdrawn from consideration as being drawn to a non-elected invention. Claims 37-58 are addressed herein.

2. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

3. This application contains claims 11-36 and 59-65 drawn to an invention nonelected with traverse in Paper No. 7. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Information Disclosure Statement

4. As set forth in the previous Office Action, the information disclosure statement filed 4/30/1999 has been placed in the application file, but the information referred to therein has not been considered, because the grandparent application 08/235,395, cited by applicant as containing such references, is unavailable. Applicant is respectfully requested to provide a copy of the references with the next correspondence, so that the examiner can consider them.

Applicant responds that a supplemental response will be filed which contains this IDS, however such response has not yet been received.

Claim Rejections Maintained

5. The rejection of claims 37-58 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained for reasons of record.

As set forth in the previous office actions, factors to be considered in determining scope and enablement are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented in the specification, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability of the unpredictability of the art, and 8) the breadth of the claims (see Ex parte Forman, 230 USPQ 546, BPAI, 1986).

The claims are broadly drawn to a method of treating a tumor in a subject and a corresponding kit comprising (a) administering a bifunctional fusion glycoprotein or conjugate thereof, wherein the glycoprotein comprises a first portion which possesses enzymatic activity, and a second portion which comprises a molecular structure that binds to a tumor specific antigen on a tumor cell, the bifunctional fusion glycoprotein or conjugate thereof having a carbohydrate complement which possesses a an "exposed carbohydrate residue" selected from mannose, galactose, N-acetylglucosamine, N-acetyllactose, glucose, and fucose; and (b) administering a second component comprising a non-toxic prodrug which is cleaved into a tumor

cytotoxic drug by the enzymatic portion of the first component. Further, the claims recite the proviso that the treatment and corresponding kit exclude the administration of an additional component that affects clearance of the first component.

Thus the method and corresponding kit encompass five broadly drawn and highly variable components. First, the enzymatic portion can be any compound, provided that it has enzymatic activity which will activate a prodrug. This includes an innumerable scope of enzymes and molecules which have enzymatic activity. Second, the molecular structure which binds a tumor specific antigen can be any antibody, ligand or other molecule, provided that it binds to any tumor specific antigen. Further, the tumor specific antigens include any antigens which are expressed or overexpressed on tumor cells. Third, a modified carbohydrate complement further broadens the scope of the method and compound. Carbohydrates are a large class of molecules, and the recitation encompasses any modification to one or many of such molecules. Fourth, the prodrug can be any inert compound which is cleaved by the enzymatic activity to have tumor cytotoxicity. This could include prodrugs of virtually any compound, including chemotherapeutics, antibiotics, etc. Fifth, the recitation of lacking an additional component which affects clearance of the first portion is of broad scope because no structural information is given, thus the component could literally be anything. Thus there are five components which are drawn to large classes of possible components, and therefor as set forth above, the claims are very broadly drawn.

The specification discloses only a single embodiment of the bifunctional fusion glycoprotein used in the method, provides no guidance as to what other bifunctional fusion glycoproteins might be used and why they might function similarly, and further gives no guidance or exemplification of the second portion (the prodrug) or clearance component which is lacking. The specification discloses only an art known fusion glycoprotein comprising a humanized variable region of Mab BW 431/26 which is linked to human beta-glucuronidase, and the galactosylation of this fusion glucoprotein. The specification further discloses administration of this galactosylated fusion glycopeptide to CEA positive xenografted mice, and that the disclosed galactosylated fusion glycopeptide is localized to the mice's CEA positive tumors and cleared from serum more efficiently than unmodified fusion glycopeptide. However, the specification does not disclose administration of any prodrug, and thus no actual treatment of tumors is modeled or exemplified, absent mere targeting of the bifunctional fusion glycoprotein to the tumor. There is not evidence or guidance that the instant method would function with a prodrug, and thus it is not clear that the instant method would inhibit or kill tumors.

The specification does not disclose any other type of enzyme, tumor binding molecule, or carbohydrate modification beyond the single exemplified embodiment. The specification fails to teach administration of any prodrug, or guidance as to what types of prodrugs would be effective or appropriate. The specification further provides no guidance as to the structure or nature of the "component which affects clearance".

Two and three component systems comprising an enzyme/tumor binding conjugate and a prodrug which is cleaved by the enzyme of the conjugate are well known in the art. The art is plagued by lack of functionality of the system, because targeting an effective amount of the first conjugate to the tumor, while retaining minimal residual conjugate in the serum, and then targeting a drug to the first conjugate so that it properly localizes and exhibits cytotoxicity only to the tumor target has proven challenging to skilled artisans.

Thus the challenge of achieving high tumor concentration, and low serum concentration is an art recognized problem. Numerous systems have been developed to shorten the serum half life of conjugates while retaining tumor targeting levels sufficient to deliver drug in a therapeutically effective amount. These techniques include administering a clearing antibody to help lower serum concentrations. The instant application seeks to eliminate the need for a clearance step by administering a conjugate which has been galactosylated and thus is cleared more rapidly. The instant application discloses the "unexpected result" that to spite rapid clearance of the first conjugate from the subject, there is still a large amount of conjugate targeted to the tumor.

However the art teaches that the instantly claimed technique does not always work, and that galactosylated targeting molecules do not localize to tumors. For example, Sharma et al., Cancer (73), pages 114-1120, February 1, 1994 teaches that a galactosylated fusion glycoprotein conjugate is rapidly cleared from the blood and no tumor localization is achieved (see page 119, first column). Further, Haisma et al., Cancer Immunology and Immunotherapy, Vol. 34, pages

343-348, teaches that with regard to bifunctional fusion glycoproteins, information on retention and tumor localization requires in vivo biodistribution studies, because the difference in clearance pattern of the conjugate is not predictable and differs with the different types of antibodies and enzymes.

Further, the specification provides no objective evidence that any other bifunctional fusion glycoprotein would function as the instantly taught single embodiment, or further that any prodrug would function effectively to treat a tumor in the instantly claimed system. The disclosure of one art known bifunctional fusion glycoprotein is insufficient support under the first paragraph of 35 U.S.C 112 for claims which encompass the innumerous bifunctional fusion glycoproteins instantly claimed, including those yet undiscovered. The courts have held that:

> "Inventor should be allowed to dominate future patentable inventions of others where those inventions were based In some way on his teachings, since some improvements while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; however, he must not be permitted to achieve this dominance by claims which are insufficiently supported and hence, not In compliance with the first paragraph of U.S.C. 112; that paragraph requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill In the art; In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad

> enablement In the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific law; In cases involving unpredictable factors, such as chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved."In re Fisher 427 F.2d 833, 166 USPQ 18 (CCPA 1970)

Further the claims encompass the complex and unpredictable field of in vivo treatment of tumors. It is well established that animal model systems do not correlate to results in patients. See for example, Osband and Ross, which teaches that mouse models are not predictive of patient response with immunotreatments (see especially page 193). See also, Time, May 18, 1998, pages 38-46, which describes the lack of correlation between effective treatment of cancer in mice versus humans, and further quotes Dr. Richard Klaus, head of the NCI as stating that "We have cured mice of cancer for decades, and it simply didn't work in people".

The specification discloses a single embodiment as described above, used to administer to xenograft mice. This is not sufficient support for the broadly claimed method of treatment and pharmaceutical composition, which encompasses treatment of humans.

Thus in light of the breadth of the claims, which is large, the state and predictability of the art, which is unpredictable, nature of the invention, which is complex, the lack of guidance and working examples, it would require undue experimentation for one of skill in the art to practice the invention as claimed.

Applicant first argues that a rejection for breadth of claims itself is not proper. Applicant further notes that the specification need not contain one or more working examples of an invention for enablement. Applicant next makes the generalized statement that "the Examiner has not demonstrated that the instantly claimed bifunctional fusion glycoproteins do not posses those characteristics which are beneficial for treating tumors." Applicant last cites page 7, lines 26-30 of the specification, which discusses in general terms how a modified carbohydrate complement enhances relative concentration of the FUP or AEC at the tumor site and increases clearance of these proteins from non-specific sites and from general circulation. Applicant thus concludes that the examiner has not met the burden of rebutting the presumptively enabled compounds.

Applicant's arguments filed 11-28-2001 have been fully considered but they are not persuasive.

It is noted by the examiner that the claims have not been rejected for the "breadth of the claims itself", or the lack of working examples but instead for the combination of the breadth of the claims, the state and predictability of the art, which is unpredictable, nature of the invention, which is complex, the lack of guidance and working examples, as set forth above. The combination of these factors is set forth to establish the case of lack on enablement. For demonstration that the instantly claimed compounds do not posses characteristics which are beneficial for treating tumors, the examiner has provided numerous references which provide examples of how the instantly claimed compounds do not function and have been plagued by

problems. Applicant has not refuted the evidence set forth by the examiner, except with a generalized statement from the beginning of the specification. Therefor the lack of enablement has been established, based on evidence set forth in the previous office action and the rejection is maintained.

Conclusion

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Hunt, whose telephone number is (703) 308-7548. The examiner can normally be reached Monday through Thursday 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (703) 308-3995. The fax number for the group is (703) 305-3014 or (703) 308-4242.

Communications via internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**anthony.caputa@uspto.gov**].

All internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists the possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist, whose telephone number is (703) 308-0196.

Jennifer Hunt

February 11, 2002

SHEELA HUFF
PRIMARY EXAMINER